TBP/TFIID-dependent activation of MyoD target genes in skeletal muscle cells.

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Public Summary:
The muscles that allow animal's to move are built predominantly of cells called myofibers. Like other specialized cell types, these myofibers develop via a regulated set of events called differentiation. In adults, this phenomenon occurs when muscles regenerate after an injury, and new myofibers differentiate from muscle stem cells that already reside within the muscles. Muscle-specific gene expression network, that underlies the identity of muscle stem cells as well as the identity of terminally differentiated skeletal myotubes, relies on the coordinated functional interactions among various protein complexes binding to regulatory regions of the muscle gens. Typically the core transcription machinery, responsible for transcribing the gene DNA sequence upon gene activation, consists in majority of cells of TFIID protein complex recognizing and activating the regulatory region of the gene. Replacement of the canonical TFIID complex with TRF3/TBP2 was reported to be required for activation of muscle-gene expression. The lack of a developmental phenotype in TBP2 null mice prompted us to further analyze whether TBP2 deficiency can compromise adult muscle development and homeostasis. We show here that TBP2 null mice have an intact regeneration potential upon injury and that TBP2 is not expressed in established C2C12 muscle cell or in primary mouse muscle stem cells. While TFIID complex is downregulated during muscle cell differentiation into myotubes, recruitment of TFIID protein complex on regulatory regions of muscle genes is essential for their expression. This evidence demonstrates that TBP2 does not replace TFIID during muscle differentiation, as previously proposed, with limiting amounts of TFIID being required to promote muscle-specific gene expression. Further studies can now explore how the TFIID-containing complex works with other regulatory protein complexes that are known to help make muscle-specific genes accessible to TFIID. These efforts will allow the various aspects of gene regulation to be integrated, which will help provide a more complete understanding of the process of muscle differentiation and regeneration.

Scientific Abstract:
Change in the identity of the components of the transcription pre-initiation complex is proposed to control cell type-specific gene expression. Replacement of the canonical TFIID-TBP complex with TRF3/TBP2 was reported to be required for activation of muscle-gene expression. The lack of a developmental phenotype in TBP2 null mice prompted further analysis to determine whether TBP2 deficiency can compromise adult myogenesis. We show here that TBP2 null mice have an intact regeneration potential upon injury and that TBP2 is not expressed in established C2C12 muscle cell or in primary mouse MuSCs. While TFIID subunits and TBP are downregulated during myoblast differentiation, reduced amounts of these proteins form a complex that is detectable on promoters of muscle genes and is essential for their expression. This evidence demonstrates that TBP2 does not replace TBP during muscle differentiation, as previously proposed, with limiting amounts of TFIID-TBP being required to promote muscle-specific gene expression.